# WEST Search History

DATE: Wednesday, June 25, 2003

| Set Name side by side | Query | Hit Count | Set Name result set |
|---|---|---|---|
| | *DB=USPT; PLUR=YES; OP=AND* | | |
| L1 | cholera or vibrio or ctx or ct or rct or toxin | 158829 | L1 |
| L2 | L1 and 29 | 50545 | L2 |
| L3 | L1 same 29 | 2774 | L3 |
| L4 | L3 and substitu$ | 1721 | L4 |
| L5 | substitu$ same 29 | 13168 | L5 |
| L6 | e29$2 | 399 | L6 |
| L7 | L6 same substitu$ | 8 | L7 |
| L8 | cholera same 29 | 88 | L8 |
| L9 | cholera near25 29 | 19 | L9 |
| L10 | mucosal | 8347 | L10 |
| L11 | L10.clm. | 726 | L11 |

END OF SEARCH HISTORY

10272987 96074761 PMID: 7490296

**Targeting of cholera toxin and Escherichia coli heat labile toxin in polarized epithelia: role of COOH-terminal KDEL.**

Lencer W I; Constable C; Moe S; Jobling M G; Webb H M; Ruston S; Madara J L; Hirst T R; Holmes R K

Combined Program in Pediatric Gastroenterology and Nutrition, Children's Hospital, Boston, Massachusetts 02115, USA.

Journal of cell biology (UNITED STATES) Nov 1995, 131 (4) p951-62, ISSN 0021-9525 Journal Code: 0375356

Contract/Grant No.: DK33506; DK; NIDDK; DK35932; DK; NIDDK; DK48106; DK; NIDDK; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

Vibrio cholerae and Escherichia coli heat labile toxins (CT and LT) elicit a secretory response from intestinal epithelia by binding apical receptors (ganglioside GM1) and subsequently activating basolateral effectors (adenylate cyclase). We have recently proposed that signal transduction in polarized cells may require transcytosis of toxin-containing membranes (Lencer, W. I., G. Strohmeier, S. Moe, S. L. Carlson, C. T. Constable, and J. L. Madara. 1995. Proc. Natl. Acad. Sci. USA. 92:10094-10098). Targeting of CT into this pathway depends initially on binding of toxin B subunits to GM1 at the cell surface. The anatomical compartments in which subsequent steps of CT processing occur are less clearly defined. However, the enzymatically active A **subunit** of CT contains the ER retention signal KDEL (RDEL in LT). Thus if the KDEL motif were required for normal CT trafficking, movement of CT from the Golgi to ER would be implied. To test this idea, recombinant wild-type (wt) and **mutant** CT and LT were prepared. The COOH-terminal KDEL sequence in CT was replaced by seven unrelated amino acids: LEDERAS. In LT, a single point **mutation** replacing leucine with valine in RDEL was made. Wt and **mutant** toxins displayed similar enzymatic activities and binding affinities to GM1 immobilized on plastic. Biologic activity of recombinant toxins was assessed as a Cl- secretory response elicited from the polarized human epithelial cell line T84 using standard electrophysiologic techniques. **Mutations** in K(R)DEL of both CT and LT delayed the time course of toxin-induced Cl- secretion. At T1/2, dose dependencies for K(R)DEL- **mutant** toxins were increased > or = 10-fold. KDEL- **mutants** displayed differentially greater temperature sensitivity. In direct concordance with a slower rate of signal transduction. KDEL- **mutants** were trafficked to the basolateral membrane more slowly than wt CT (assessed by selective cell surface biotinylation as transcytosis of B **subunit** ). **Mutation** in K(R)DEL had no effect on the rate of toxin endocytosis. These data provide evidence that CT and LT interact directly with endogenous KDEL-receptors and imply that both toxins may require retrograde movement through Golgi cisternae and ER for efficient and maximal biologic activity.

Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

08698782 95387387 PMID: 7658465

**Immunoglobulin** mutant **library genetically screened for folding stability exploiting bacterial signal transduction.**

Kolmar H; Frisch C; Gotze K; Fritz H J
Institut fur Molekulare Genetik, Gottingen, F.R.G.

Journal of molecular biology (ENGLAND) Aug 25 1995, 251 (4) p471-6, ISSN 0022-2836 Journal Code: 2985088R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS

A model repertoire of variants of immunoglobulin kappa variable **domain** REIv with different folding stabilities was generated by oligonucleotide-directed randomization of position **29** , a key conserved residue of hypervariable loop 1. Fused to ToxR', the membrane-anchored cytoplasmic **domain** of the **Vibrio** cholerae ToxR transcription activator, different members of the library induce different levels of transcription from the ctx promoter in Escherichia coli. Differences in transcription activation correlate positively with folding stabilities of the corresponding REIv **domains** . Since conformationally stabilized REIv derivatives elicit a dark red colony phenotype on EMB-lactose indicator plates, this procedure constitutes a genetic screen for immunoglobulin folding stability.

Descriptors: DNA-Binding Proteins--genetics--GE; *Gene Library; *Immunoglobulins, kappa-Chain--genetics--GE; *Protein Folding; *Signal Transduction; *Transcription Factors--genetics--GE; * **Vibrio** cholerae --chemistry--CH; Amino Acid Sequence; Base Sequence; **Cholera Toxin** --genetics--GE; Escherichia coli--genetics--GE; Genes, Bacterial--genetics --GE; Genes, Immunoglobulin--genetics--GE; Immunoglobulin Variable Region --chemistry--CH; Immunoglobulin Variable Region--genetics--GE; Immunoglobulins, kappa-Chain--chemistry--CH; Molecular Sequence Data; **Mutagenesis** , Site-Directed; Recombinant Fusion Proteins--chemistry--CH; Trans-Activation (Genetics); beta-Galactosidase--genetics--GE; beta-Lactamases

CAS Registry No.: 0 (DNA-Binding Proteins); 0 (Immunoglobulin Variable Region); 0 (Immunoglobulins, kappa-Chain); 0 (Recombinant Fusion Proteins); 0 (Transcription Factors); 114265-38-2 (ToxR protein); 9012-63-9 (Cholera Toxin)

Enzyme No.: EC 3.2.1.23 (beta-Galactosidase); EC 3.5.2.6 (beta-Lactamases)

Gene Symbol: ctx

Record Date Created: 19951002

Record Date Completed: 19951002

07523500 92387231 PMID: 1381311

**The adjuvant effect of** Vibrio **cholerae and Escherichia coli heat-labile enterotoxins is linked to their ADP-ribosyltransferase activity.**

Lycke N; Tsuji T; Holmgren J

Department of Medical Microbiology and Immunology, University of Goteborg, Sweden.

European journal of immunology (GERMANY) Sep 1992, 22 (9) p2277-81, ISSN 0014-2980 Journal Code: 1273201

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

This study addressed the question of whether the mucosal adjuvant property of cholera toxin (CT) and the structurally closely related Escherichia coli heat-labile toxin (LT) requires the enterotoxic and adenylate cyclase/cAMP activating property of these molecules. Therefore, we investigated the cytotoxic and adjuvant abilities of the enterotoxins and compared the results with those obtained with the non-toxic CT and LT derivatives; recombinant CTB (rCTB) and a mutated LT (mLT), which had a single amino acid **substitution** in position 112 (Glu----Lys) of the A **subunit** . Detailed functional studies revealed that, in contrast to the enterotoxins, both rCTB and mLT lacked ADP-ribosylating and cAMP-stimulating abilities. However, similar membrane ganglioside GM1-receptor binding ability of all the putative adjuvants was demonstrated. When the probe antigen, keyhole limpet hemocyanin (KLH), was given perorally together with CT or LT strong gut mucosal anti-KLH immune responses were stimulated, whereas no or very low anti-KLH responses were seen in the groups which received antigen admixed with rCTB or the mLT. Moreover, the specific serum antibody responses to the various immunization protocols closely paralleled the local anti-KLH response in the gut. From these results it appears that the adjuvant mechanism of LT, and probably also of CT, is linked to the ability to ADP-ribosylate and to stimulate cAMP formation. However, this study does not unequivocally rule out other possibilities such as interactions by the A1 fragment of CT or LT with other G-proteins than Gs alpha or events that parallel or precede the effects on the adenylate cyclase/cAMP system. Thus, the levels of ADP-ribosylation and cAMP-induction that are required and the key event or target cell that is responsible for the adjuvant effect of CT and LT remain to be elucidated. Studies are underway to address these issues.

Tags: Animal; Female; Support, Non-U.S. Gov't

Descriptors: **Adjuvants, Immunologic** --pharmacology--PD; *Bacterial Toxins--pharmacology--PD; * **Cholera Toxin** --pharmacology--PD; *Enterotoxins --pharmacology--PD; *Poly(ADP-ribose) Polymerases--pharmacology--PD; Cyclic AMP--biosynthesis--BI; Epitopes--analysis--AN; Hemocyanin--immunology--IM; Mice; Mice, Inbred C57BL; Rabbits

CAS Registry No.: 0 (Adjuvants, Immunologic); 0 (Bacterial Toxins); 0 (Enterotoxins); 0 (Epitopes); 0 (enterotoxin LT); 0 (keyhole-limpet hemocyanin); 60-92-4 (Cyclic AMP); 9012-63-9 (Cholera Toxin); 9013-72-3 (Hemocyanin)

Enzyme No.: EC 2.4.2.30 (Poly(ADP-ribose) Polymerases)

Record Date Created: 19921007

Record Date Completed: 19921007

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File 440:Current Contents Search(R)  1990-2003/Jun 25
       (c) 2003 Inst for Sci Info

      Set  Items  Description
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Executing TD717
>>>SET HILIGHT: use ON, OFF, or 1-5 characters
              62  AU=GLINEUR?
             517  AU=LOCHT?
           13830  CHOLERA?
      S1       4  (AU=GLINEUR? OR AU=LOCHT?) (100N) CHOLERA?
?t s1/6,kwic/all
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WEST

## Search Results - Record(s) 1 through 6 of 6 returned.

L2: Entry 1 of 6 File: USPT May 13, 2003

US-PAT-NO: 6562614
DOCUMENT-IDENTIFIER: US 6562614 B2

TITLE: ADP-ribosylation factor-like proteins

DATE-ISSUED: May 13, 2003

US-CL-CURRENT: 435/255.1; 435/255.2, 435/471

INT-CL: [07] C12 N 1/14, C12 N 15/74

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L2: Entry 2 of 6 File: USPT May 13, 2003

US-PAT-NO: 6562352
DOCUMENT-IDENTIFIER: US 6562352 B1

TITLE: Vaccine compositions for mucosal delivery

DATE-ISSUED: May 13, 2003

US-CL-CURRENT: 424/240.1; 424/253.1, 424/254.1, 424/434, 424/435

INT-CL: [07] A61 K 39/10, A61 F 13/00

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L2: Entry 3 of 6 File: USPT Nov 26, 2002

US-PAT-NO: 6486168
DOCUMENT-IDENTIFIER: US 6486168 B1

TITLE: Formulations and methods for treatment of mucosal associated conditions with an immune response modifier

DATE-ISSUED: November 26, 2002

US-CL-CURRENT: 514/293

INT-CL: [07] A61 K 31/44

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L2: Entry 4 of 6 File: USPT Feb 19, 2002

US-PAT-NO: 6348449
DOCUMENT-IDENTIFIER: US 6348449 B1

TITLE: Methods of inducing mucosal immunity

DATE-ISSUED: February 19, 2002

US-CL-CURRENT: 514/44; 424/130.1, 424/184.1, 424/209.1, 435/235.1, 435/252.3, 435/320.1, 435/455, 514/2, 514/330

INT-CL: [07] A01 N 43/04, A61 K 31/70

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L2: Entry 5 of 6 File: USPT Aug 7, 2001

US-PAT-NO: 6270758
DOCUMENT-IDENTIFIER: US 6270758 B1

TITLE: Substantially non-toxic biologically active mucosal adjuvants in vertebrate subjects

DATE-ISSUED: August 7, 2001

US-CL-CURRENT: 424/85.2; 424/184.1, 424/198.1, 424/278.1, 530/351

INT-CL: [07] A61 K 45/00, A61 K 39/00, A61 K 47/00, C07 K 1/00, C07 K 14/00

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L2: Entry 6 of 6 File: USPT Nov 21, 2000

US-PAT-NO: 6149919
DOCUMENT-IDENTIFIER: US 6149919 A

TITLE: Immunogenic detoxified mutants of cholera toxin and of the toxin LT, their preparation and their use for the preparation of vaccines

DATE-ISSUED: November 21, 2000

US-CL-CURRENT: 424/236.1; 424/184.1, 424/234.1, 424/240.1, 424/241.1, 424/257.1, 424/261.1, 435/69.3

INT-CL: [07] A61 K 39/02, A61 K 39/108, A61 K 39/106, C12 P 21/06

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